

## Tozinameran (Pfizer-BioNTech COVID-19 vaccine)-induced AGEP-DRESS syndrome

### Dear Editor,

A 40-year-old woman with scalp psoriasis was maintained on topical mometasone furoate therapy from 2019 with no major psoriatic flares until she presented with one week of an acute generalised pustular eruption and fever in June 2021. Physical examination revealed numerous discrete and confluent pustules studded on her scalp, trunk and limbs, on a background of suberythroderma (Fig. 1). Laboratory investigations were significant for eosinophilia ( $1.21 \times 10^3/\mu\text{L}$ , reference  $0.03\text{--}0.77 \times 10^3/\mu\text{L}$ ) and transaminitis (AST 65 IU/L, reference 2–32 IU/L, ALT 66 IU/L, reference 2–32 IU/L). She had received 2 doses of tozinameran

(Pfizer-BioNTech COVID-19 vaccine), given 11 and 7 weeks prior, and had not used other medications in the preceding 3 months. She had no family or personal history of a drug hypersensitivity reaction. Polymerase chain reactions for human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were negative.

A biopsy of the right forearm pustule showed subcorneal pustules containing neutrophils, spongiosis and a superficial perivascular infiltrate of numerous eosinophils with dermal oedema (Fig. 2). She was treated with prednisolone 30mg daily tapered over 4 weeks and intensive topical 0.05% clobetasol propionate

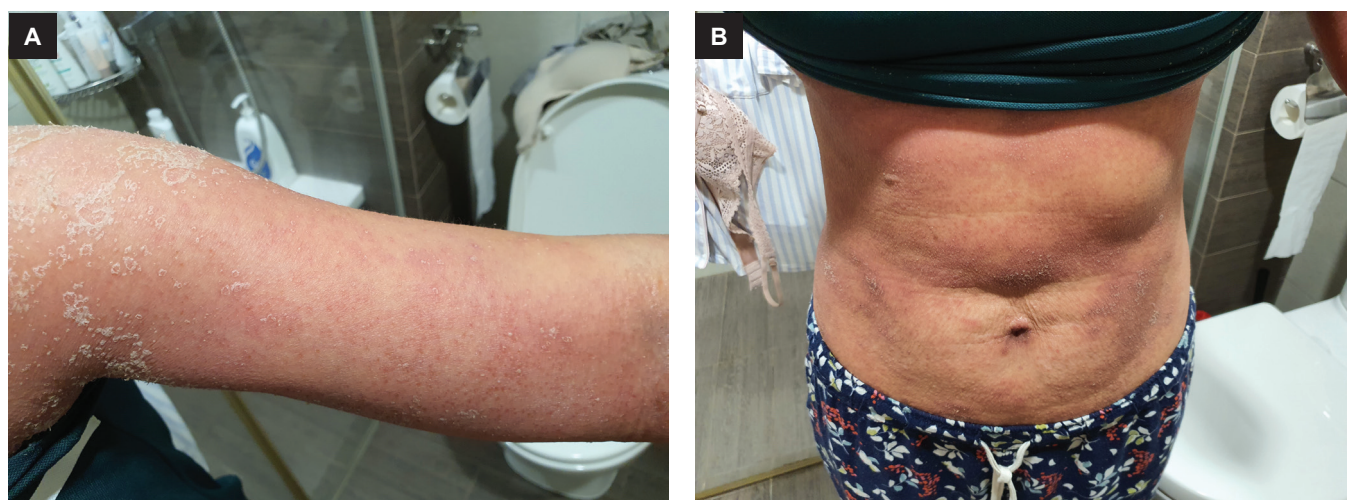


Fig. 1. (A) Clinical photograph showing both discrete and confluent pustules in the left arm, and (B) extensive exanthem in trunk with both discrete and confluent pustules.

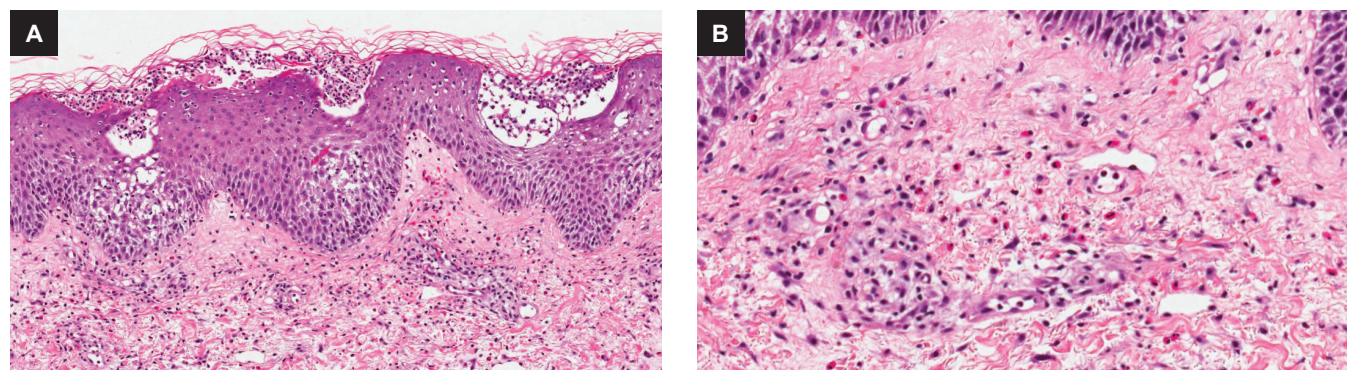


Fig. 2. Skin biopsy from the right forearm showing a basketweave stratum corneum with subcorneal pustules containing neutrophils. (A) The epidermis shows spongiosis, and the dermis a superficial perivascular infiltrate of lymphocytes with many eosinophils (haematoxylin and eosin stain: 100x magnification). (B) There are increased numbers of eosinophils within the dermis (haematoxylin and eosin stain: 200x magnification).

cream twice daily. There was a near resolution of symptoms and normalisation of eosinophilia and transaminitis after 2 months.

The initial provisional diagnosis was an acute generalised pustular psoriasis (GPP) flare. However, as the disease progressed, features not in keeping with GPP such as serum eosinophilia and histological perivascular infiltrates of eosinophils were seen. Instead, the long latency, protracted course of the disease, fever and systemic involvement supported the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Though pustules are reported in DRESS, the consistent histopathological findings with the presence of discrete and confluent pustules were more typical of acute generalised exanthematous pustulosis (AGEP). The RegiSCAR score for DRESS in this patient was 4 (probable, scored as such: no fever  $>38.5^{\circ}\text{C}$  = -1, presence of eosinophilia = 1, skin rash = 2, organ involvement = 1, exclusion of other causes = 1) and EuroSCAR score for AGEP was 5 (probable, scored as such: typical pustules = 2, typical erythema = 2, typical distribution = 2, post-pustular desquamation = 1, no acute onset = -2, no resolution  $<15$  days = -4, fever = 1, histology of spongiform subcorneal pustules with papillary oedema = 3).<sup>1,2</sup> As the patient had some features consistent with both, we favoured the diagnosis of acute generalised exanthematous pustulosis (AGEP)-drug reaction with eosinophilia and systemic symptoms (DRESS) overlap syndrome secondary to tozinameran. AGEP-DRESS overlap syndrome is not a new entity, and it has been reported in association with another COVID-19 vaccine, Janssen Ad26.COV2.S, a recombinant-vector vaccine.<sup>3</sup>

We opine that in our patient, tozinameran instigated an overly robust host response, leading to a cytokine imbalance syndrome, and precipitated an AGEP-DRESS overlap syndrome. This delayed cutaneous manifestation may be related to the host immune cytokine response rather than true allergies, an observation similar to Juay et al. in their 3 cases of vesiculobullous cutaneous reactions to tozinameran.<sup>4</sup> Other vaccines, such the MMR vaccine, have also been previously demonstrated to exacerbate atopic dermatitis via elevated IL-4 levels, disrupting the Th1 and Th2 lymphocytic balance.<sup>5</sup> COVID-19 vaccinations have been reported in association with many cutaneous

side effects in many local institution-based studies.<sup>6,7</sup> However, AGEP-DRESS overlap syndrome has thus far neither been observed in association with primary SARS-CoV-2 viral infection, nor after tozinameran vaccination. Further patho-immunological studies should follow to better establish the causal association of tozinameran and DRESS syndrome.

In conclusion, it is important for dermatologists to consider mRNA COVID-19 vaccine as a potential culprit agent in patients presenting with AGEP and/or DRESS syndrome, as illustrated by this case. The safety of future mRNA COVID-19 vaccinations for such patients will need to be reviewed as well.

## REFERENCES

1. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
2. Sidoroff A, Halevy S, Bavinck JNB, et al. Acute generalized exanthematous pustulosis (AGEP) - A clinical reaction pattern. *J Cutan Pathol* 2001;28:113-9.
3. Lospinoso K, Nichols CS, Malachowski SJ, et al. A case of severe cutaneous adverse reaction following administration of the Janssen Ad26.COV2.S COVID-19 vaccine. *JAAD Case Rep* 2021;13:134-7.
4. Juay L, Chandran NS. Three cases of vesiculobullous non-IgE-mediated cutaneous reactions to tozinameran (Pfizer-BioNTech COVID-19 vaccine). *J Eur Acad Dermatology Venereol* 2021;35:e855-7.
5. Olesen AB, Juul S, Thestrup-Pedersen K. Atopic Dermatitis Is Increased Following Vaccination for Measles, Mumps and Rubella or Measles Infection. *Acta Derm Venereol* 2003; 83:445-50.
6. Tan JTC, Tan C, Teoh J, et al. Adverse reactions and safety profile of the mRNA COVID-19 vaccines among Asian military personnel. *Ann Acad Med Singap* 2021;50:827-37.
7. Lim SM, Chan HC, Santosa A, et al. Safety and side effect profile of Pfizer-BioNTech COVID-19 vaccination among healthcare workers: A tertiary hospital experience in Singapore. *Ann Acad Med Singap* 2021;50:703-11.

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